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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,361	10/11/2001	Lawrence A. Rheins	DERM1100-5	2313

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,361	RHEINS ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/01, 11/18/02, 4/14/2003, 06/06/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In instant application, the first sentence of the specification claims priority to U.S. Application 09/375609 but there is no statement that the instant application is a divisional of U.S. Application 09/375609.

Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Method for detection of biological factors in the epidermis" is not descriptive because there are no

claims directed to methods of detection of biological factors. The claims are all directed to a method of diagnosing ACD (allergic contact dermatitis) in a subject.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention 2) state of prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working templates, 6) breadth of claims, 7) amount of direction of guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(a) Claims 1-7 are drawn towards diagnosis of ACD, "wherein an elevated amount of IL-13 is indicative of ACD". The specification (in Tables 2 and 3) teaches that

the ratio of IL-13 mRNA to GADPH is detected at a higher level after 48 hours of allergen exposure, than is detected after 72 hours of irritant exposure, or in normal skin. Therefore, in order to diagnose ACD (and not ICD) in a subject, IL-13 mRNA must necessarily be quantitated after 48 hours of exposure. However, while applicants disclose the quantity of IL-13 mRNA after 72 hours of irritant exposure, there is no disclosure of the quantity of IL-13 mRNA after 48 hours of irritant exposure. Due to the high level of unpredictability in the art (set forth in the following paragraph) suggesting several other IL mRNA levels can rise and fall over time after allergen exposure, and in the absence of other evidence suggesting IL-13 mRNA levels are stable over time after exposure, it is not predictable what the levels of IL-13 mRNA will be after 48 hours of irritant exposure. To use the instantly claimed method would require undue experimentation to determine if the 48 hour time point is diagnostic, and if so, what levels of IL-13 mRNA would be diagnostic.

The teachings of Kondo (reference AN cited in the IDS of 11/20/2002) indicate that the levels of epidermal cytokine mRNA vary significantly over time following exposure to an allergen or irritant. In particular, Kondo teaches that in mice, ACD was characterized by an initial suppression in IL-Iα levels followed by an increase in 1L-1α mRNA levels at 12 to 24 hours following exposure to hapten and that IL-1β, IL-6, 1L- 10 and GM-CSF mRNA levels did not increase until 6 hours after exposure to a hapten. In addition, Kondo teaches that in ICD, 1L-1 mRNA levels were upregulated 1 hour following exposure to a hapten, but then were suppressed 3-24 hours following exposure. Furthermore, Kondo teaches that at 24 hours following exposure to a hapten

IL-1β, IL-6, IL-l0 and GM-CSF mRNA levels were increased in both ICD and ACD, and thereby levels of these cytokines at 24 hours could not be used to distinguish between ICD and ACD. Kondo teaches (page 372) that it is important to select the appropriate time points and to look at the entire time course of the reaction to elucidate markers to differentiate ACD and ICD. Grangsjo (reference AB cited in the IDS of 6/09/2003) also highlights the unpredictability in the art of detecting the level of cytokine as indicative of response to irritants in that Grangsjo reports that the cytokine response in ICD may be time and substance dependent. Specifically, Grangsjo found that nonanoic acid (NAA), but not SLS induced an increase in IL-6 mRNA levels, whereas SLS, but not NAA, induced an increase in GM-CSF levels.

(b) Claims 1-4 encompass any cell isolated from a subject. Even if these claims were enabled for methods of detecting mRNA in skin cells (see above), they would not be enabled for cells other than skin cells. In the absence of other evidence in the specification, it is not predictable that ACD could be diagnosed by using cells other than skin cells. No working examples are provided in the specification of methods of diagnosis using cells other than skin cells. What is missing from the specification is a disclosure of the quantity of cytokine mRNAs necessary to diagnosis ACD in cells other than skin cells. It is not predictable that mRNA levels would change in non-affected tissues. To use the instantly claimed method would require undue experimentation to determine in which cell types the quantity of cytokine mRNA present in cells would be indicative of ACD.

(c) Claims 1-7 are further not enabled in a manner commensurate in scope with the claims because they encompass the detection of DNA. While the prior art appreciates the detection of RNA, specifically mRNA as an indicator of expression of cytokines (or other proteins), the DNA that is transcribed to make the mRNA would not be expected to be present in any different quantity when the gene is expressed, as opposed to when it is not. It is not accepted in the art that cytokine expression happens via DNA amplification; rather the DNA is transcribed to make mRNA, which is translated to make protein. Amplification (the production of protein in an amount disproportionate to the amount of DNA present) can happen either at the transcription or translation step, and often at both, but not by DNA amplification. Accordingly, since the person of ordinary skill in the art would not accept that DNA levels would be indicative of cytokine expression, and as the specification provides no guidance nor working examples of such, the specification is not enabling of detection of DNA for diagnosis or distinguishment of inflammatory reactions or any other disorder not directly associated with a change in the DNA itself.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in that it recites the acronym ACD (allergic contact dermatitis). Use of acronyms results in indefinite language because the acronyms used to define proteins can be subject to change or reference more than one protein. Therefore, when used for the first time scientific terms should be completely spelled out.

Claim 1 is also indefinite because the recitation "...wherein an elevated amount of IL-13 is indicative of ACD" fails to specify sufficient method steps to allow diagnosis of ACD. It is not clear whether an elevated amount of IL-13 mRNA is in reference to normal skin cells, or skin cells exhibiting an ICD reaction. The claims do not set forth a comparison step in which levels are compared to a control or reference value.

Claim 1 is also indefinite because the recitation "...wherein an elevated amount of IL-13 is indicative of ACD" is unclear as to whether the applicant is referring to the amount of IL-13 polynucleotide or protein. In regard to this matter, this claim would be definite if Applicant amended the portion of the claim to read, "...wherein an elevated amount of mRNA encoding IL-13 is indicative of ACD". Claims 2-4 are indefinite for the same reason but would be made definite if Applicant amended each claim to read "...wherein the mRNA encoding IL-13 is detected by..."

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan (reference AH cited in the IDS of 4/14/2003) in further view of Xu #1 (1996, Toxicology Methods, 6: 23-31) and Xu #2 (April 1997, Toxicology Methods, 7:137-148).

Paludan teaches (on page 834, column 2) "our technique has proved useful for discriminating between epidermal IL-8 mRNA levels in a variety of inflammatory skin diseases and reactions (Fig 5, Table II) and should be applicable to analysis of other cytokine mRNAs and other skin compartments." Paludan quantifies IL-8 mRNA by a "quantitative PCR method" (described in the Materials and Methods section starting on page 830). This PCR method includes (as described on page 831) primers which hybridize with the mRNA to be detected. Table II shows the results of quantitative IL-8/GADPH mRNA ratios in positive allergic patch-test reactions as compared with diseases, other induced skin reactions, and normal skin in human subjects. These results show that the positive allergic patch-test reaction is characterized by an elevated quantity of IL-8 mRNA over normal skin. Positive allergic patch-test reactions are an accepted model of allergic contact dermatitis because the patch test reaction involves contacting skin with an allergen that induces dermatitis. A method of discriminating an allergic reaction from other skin diseases and reactions in a subject is equivalent to diagnosing ACD in subject, because diagnosis of ACD necessarily requires distinguishing an allergic reaction from other skin diseases and reactions. While Paludan teaches diagnosis of ACD by quantitating mRNA encoding IL-8, Paludan does

not teach diagnosis of ACD by quantitating mRNA encoding IL-13. Xu #1 teaches (on page 26), "As presented in Figure 2...the mRNAs for IL-2, IL-4, and IFN-gamma were not detected in the control mice, but were confirmed in the skin of mice with allergic contact dermatitis to DNCB." Xu #2, on page 146, makes reference to the results of Xu #1, and then states, "similar to IL-4, the expression of IL-13 mRNA was detected in skin sites of mice with contact allergy to picryl chloride and OXAZ (our unpublished data)."

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute quantitation of mRNA encoding IL-13 for the quantitation of mRNA encoding IL-8 taught by Paludan. The person of ordinary skill in the art would have been motivated to make that modification because Paludan teaches their technique is applicable to analysis of other cytokine compartments, Xu #1 and Xu #2 together teach that IL-13 is present in allergic contact dermatitis but absent in normal skin and therefore that quantitation of IL-13 mRNA would indicate a diagnosis of ACD.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paludan in further view of Xu #1, Xu #2, and Torrence, US Patent 5,583,032. As described above, Paludan, Xu #1, and Xu #2 teach all of the limitations of claim 2. These references do not teach detecting the polynucleotide by RNase protection assay. As described above, Paludan teaches PCR as a method of detecting mRNA of skin cytokines to use in distinguishing skin conditions. Torrence teaches (in paragraph 202) use of RNase protection assays to detect polynucleotides as an independent and quantitative method to confirm detection of mRNA by a PCR method. It would have been obvious to the person of ordinary skill in the art at the time the invention was made

to substitute RNase protection assays to detect polynucleotides for the PCR method taught by Paludan. The person of ordinary skill in the art would have been motivated to make that modification because Torrence teaches RNase protection assay as a method to independently confirm quantitative PCR results, and in the absence of any evidence to the contrary, identical results would be expected using this method for IL-13 mRNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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